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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,706	04/10/2002	Guillermo De La Cueva Mendez	620-180	8608

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EXAMINER	
GANGLE, BRIAN J	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/030,706	DE LA CUEVA MENDEZ ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,10,12-16 and 18* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 10, 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/1/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and remarks, filed 12/15/2006, are acknowledged. Claims 1-4, 10, 12-16, and 18 are currently pending. Claim 18 is withdrawn as being drawn to a nonelected invention. Claims 1-4, 10, and 12-16 are currently under examination.

Information Disclosure Statement

The information disclosure statement filed 5/1/2006 has been considered. An initialed copy is enclosed.

Claim Rejections Withdrawn

The rejection of claims 1-17 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting cell proliferation which include inhibiting cell cycle progression in eukaryotic cells *in vivo*, does not reasonably provide enablement for said method in all eukaryotic cells as claimed, is withdrawn in lieu of the rejection set forth below.

The rejection of claims 1-10 and 12-16, as being rendered vague and indefinite by the phrases "a method of inhibiting cell proliferation and/or cell cycle progression," "target cells," "an inhibitor of said toxin, optionally and antidote to the toxin wherein both toxin and antidote are proteins, under appropriate control for cell cycle inhibition," is withdrawn in light of applicant's amendments thereto.

The rejection of claims 10 and 12-16, as being rendered vague and indefinite by the phrase "a method of inhibiting cell proliferation and/or cell cycle progression," is withdrawn in light of applicant's amendments thereto.

The rejection of claims 2-10 and 12-17 because they recite the indefinite article "A" meaning any product or method, but then attempt to limit the method/product to a particular product form or method steps is withdrawn in light of applicant's amendments thereto.

The rejection of claims 11-17 as being rendered vague and indefinite by the phrase "a method of inhibiting cell proliferation and/or cell cycle progression," is withdrawn in light of applicant's amendments thereto.

The rejection of claims 12-16 because it is not clear whether the phrase "controlling activity of said antidote" is meant to be an active step or a further limitation of the "appropriate control" in claim 1 is withdrawn in light of applicant's amendments thereto.

The rejection of claims 12-16 because the phrase "controlling activity" lacks antecedent basis, is withdrawn in light of applicant's arguments.

The rejection of claims 1-6 and 10-11 under 35 U.S.C. 102(b) as being anticipated by Molin *et al.* (US Patent 5,670,370, 1997), is withdrawn in light of applicant's amendments thereto.

The rejection of claims 1, 2, 6, 10, and 12-16 under 35 U.S.C. 102(b) as being anticipated by Paulus *et al.* (J. Neurosurg. 87:89-95, 1997), is withdrawn in light of applicant's amendments thereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claim 4 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained for the reasons set forth in the previous office action.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues: that applicant's have shown that the kid/kis system can be used to selectively control cell cycle progression and cell proliferation both *in vivo* and *in vitro* in a variety of eukaryotic cells, including human cells. The "variety of eukaryotic cells" includes yeast and human cells *in vitro*, *Xenopus* embryos, and zebrafish embryos. Applicant argues that

zebrafish are known to be useful model organisms for use in investigating diseases and treatments of mammals, that zebrafish have many of the same organs as mammals, and that most human genes have homologs in zebrafish. Therefore, the showing that kis/kid can be introduced into zebrafish under appropriate control to bring about selective killing of cells is predictive that the same is true in mammals, including humans.

Applicant's arguments have been fully considered and deemed non-persuasive.

Claim 4 is drawn to *therapeutic* use of the kid/kis system in humans or animals. The term therapeutic encompasses all diseases or conditions that afflict humans and animals. The fact that one can successfully introduce kid/kis into cells does not in any way imply that a particular disease can be treated. For example, there is no reason to believe that selectively killing eukaryotic cells would be therapeutic for a disease caused by bacterial growth. In addition, the *in vivo* data is limited to the introduction of kid/kis into one or two-cell stage embryos, so that the progeny of the injected cell contains the genes for kid/kis. Applicants have not shown any way that particular cells (such as tumor cells or other cells which should be controlled to achieve a therapeutic result) in a developed organism could be targeted; nor have applicants shown what cells need to be controlled in order to treat any particular disease. Regarding applicant's assertion that zebrafish are useful models for human disease, as stated above, the claim encompasses all human diseases. While zebrafish might be a model for some human diseases, they certainly have not been shown to be good models of diseases such as AIDS, Alzheimer's, or gonorrhea. Further, the only *in vivo* methods shown by applicant have involved manipulation of one or two-celled embryos. It has not been shown that creating a transgenic human by manipulating one or two-celled embryos is effective in any therapeutic capacity.

As outlined previously, claim 4 is drawn to a method of claim 1 which is therapeutic and carried out on a human or animal body. The art has shown no examples of such a method being successful. The use of bacterial toxins alone, such as diphtheria toxin, has been proposed as a method of treating cancer, however, there have only been successes with *in vitro* studies or in mice models (Fitzgerald, Semin. Cancer Biol, 7:87-95, 1996, p. 93). Further, these studies involved injecting tumors with toxin, and did not follow the method of the instant application using an antitoxin or the specific embodiment of providing the toxin by expressing it within the

cells. Diphtheria toxin has been used to control eukaryotic cell growth using transcriptional control elements, however, this work was only *in vitro* (Paulus *et al.*, J. Neurosurg., 87:89-95, 1997; Massuda *et al.*, Proc. Natl. Acad. Sci. USA, 94:14701-14706, 1997). The art also teaches that while the use of toxins to control eukaryotic cell growth (especially cancer) is promising, there are hurdles to be overcome. Vassaux *et al.* (Breast Cancer Res., 2:22-27, 2000) states that clinical use of genetic toxins would require efficient and reliable targeting of cancer cells, and that this cannot be achieved with current tools (p. 22, col. 1). Fitzgerald *et al.* also state that two problems in particular must be overcome to use toxins. First, administration of toxins to humans has led to unanticipated toxicity in normal tissue, and second, the human immune response limits the effects of the toxin (p. 93, col. 1, paragraph 2). The only guidance the specification provides is to state that compositions of the toxin-antitoxin may be administered to individuals, preferably in "therapeutically effective amounts." The specification further states that the amount, rate, and time-course of administration will depend on the nature and severity of what is being treated (p. 33. lines 5-15). There are no examples or data to show any therapeutic effect of any embodiments of the present invention, either in an animal model, or humans. In view of the lack of support in the art and specification, it would require undue experimentation to use the method as claimed; therefore the claim is not enabled.

New Claim Rejections

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 10, and 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods in a target eukaryotic cell *in vitro*, does not reasonably provide enablement for the methods as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of inhibiting cell proliferation in target eukaryotic cells by providing within said cells, ParD kid toxin and ParD kis antitoxin, under appropriate control for selective cell cycle inhibition and/or killing of said targets cells.

Breadth of the claims: The claim encompasses all eukaryotic cells, including human cells, and both *in vivo* and *in vitro* use of said method.

Guidance of the specification/The existence of working examples: The specification discloses examples where kid/kis genes are introduced into yeast and human cells *in vitro*, and where said genes were introduced into a single cell of a two-cell stage *Xenopus* embryo. The method using *Xenopus* is regarded by applicant as an *in vivo* method.

State of the art: First, administration of toxins to humans has led to unanticipated toxicity in normal tissue, and second, the human immune response limits the effects of the toxin (p. 93, col. 1, paragraph 2). While the specification provides examples of the method using cells

in vitro, there is no evidence to show that the method could be used successfully in humans. Further, the specification does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said toxins are administered *in vivo* to control cell proliferation in tumor or other cells, although *in vivo* use is clearly encompassed by the claims. The specification is lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* data as exemplified in the instant specification with *in vivo* benefit. Hence, the specification cannot be said to teach how to use the claimed toxins in all eukaryotic cells without undue experimentation. Moreover, while those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are somewhat useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Moreover, Dermer (Bio/Technology, 1994, Vol. 12 page 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable

and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly, it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Further, neither applicant nor the art has shown a predictable method of delivering the kid/kis genes to multiple cells, or to specific cells in a developed organism so that the target cells can be controlled. The only *in vivo* methods shown by applicant have involved manipulation of one or two-celled embryos. This can hardly be considered an *in vivo* method. While these embryos do grow into organisms, it has not been shown how to target cells in the developed organism. Further, it has not been shown that creating a transgenic human by manipulating one or two-celled embryos would lead to predictable results. It is also noted that the claims encompass delivery of kid/kis by the introduction of the kid/kis genes, but also by introduction of the toxin and antitoxin themselves. There is no means provided in either the art or the specification to administer these proteins to target cells *in vivo*; nor is there a means provided for controlling the activity of these proteins.

Therefore, in view of the lack of support in the art and specification for the use of the method with all eukaryotic cells, it would require undue experimentation to use the full scope of the method as claimed; and the entire scope of the claim is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 10, and 12-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite by the phrase "under appropriate control for selective cell cycle inhibition and/or killing of said target cells." First, as evidenced by Pimentel *et al.* (EMBO J., 24:3459-3469, 2005), kid exerts a reversible cytostatic effect. Therefore, it is

not clear how using the kid toxin would lead to killing of target cells rather than cell cycle inhibition of said cells. Second, the limitations engendered by the term "appropriate" are not clear. What are the requirements for something to be "appropriate"?

Claim 4 is rendered vague and indefinite by the phrase "carried out on a human or animal body." It is not clear whether the term "on" is meant to include the entire animal body, or only the surface of the body.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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